DESTINATION DISCOVERY
Oct. 1994, pp. 14-19

SNAPSHOTS FROM THE BRAIN: HOW MEMORIES ARE MADE
by Mark Wheeler

You Remember Your First Kiss from School Days, but Can't for the Life of You Remember Where You Put Your Glasses Fifteen Minutes Ago. Forget High School Biology--Science Is Getting a Clearer and Clearer Picture of Why Certain Bits of Everyday Life Get Stored, and Others Don't.

The heart may beat, the lungs may heave, the blood may flow, but memories are the stuff of life.

H.M. was just twenty-seven when surgeons decided to remove a chunk of his brain. Several chunks, actually, including the temporal lobes located behind the ears, another called the hippocampus situated nearby, and still another close at hand called the amygdala.

This was risky business in 1953. While brain surgery is still no snap today, forty-some years ago very little was understood about how the brain worked and how its parts interacted. But H.M.'s doctors were desperate--he was an epileptic whose seizures were increasing in frequency, incapacitating him. Because they thought the seizures were coming from those specific areas of the brain, they removed them, hoping to bring him some blessed relief.

To most of us hearing this tale, H.M. is a sad story, but to neurobiologists who are struggling to understand the biological basis of memory, H.M. is a famous case history. For God, or biology, or both played a cruel joke on H.M. The surgery did indeed stop the bulk of his seizures. But it also robbed him of his ability to form new memories. After the surgery, when he was asked about his childhood or youth, H.M. could recall about the same as the average person. To this day, though, when asked about the magazine he's just read or a meal he's just eaten, H.M. has no recall at all. Just moments after meeting someone new, he'd completely forget the person. He lived with his parents, but when they moved to a new house, it took him eight years to learn its floor plan. Since learning is the process we use to procure new knowledge and facts, and memory the tool that helps us retain that knowledge over time, H.M. was badly cheated because he couldn't retain facts.

He was, though, able to learn a few things. For example, he learned the "mirror drawing task," a test in which you trace an object using a mirror. You can't see what you are drawing, or your hand, directly. Instead you view both by watching a mirror. As a result, the natural tendency is to trace the object backward. With practice, however, mirror-drawing can be learned. This type of learning is a visual motor task, an implicit memory. H.M. could be taught new motor skills like this, but could never recall the act of learning such skills.

This loss of memory was, of course, tragic for H.M., who, since the death of his parents, now lives in a Connecticut nursing home. But the unanticipated results of his surgery also provided scientists with early clues about memory storage and retrieval. H.M. provided researchers with early evidence that the hippocampal area is vital in forming new long-term memories, but isn't used to retrieve memories that had been previously filed away; these memories are formed in one section of the brain, and stored in another. And he showed that more than one type of memory exists--short-term and long, explicit (the kind you use when consciously learning a fact) and implicit (walking, catching a ball,

and other such motor skills), and several in between.

While the experiences of patients like H.M. shed some light on how memory functions, it's only been in the last fifteen years or so that scientists have begun to understand some of its basic workings. The principal reason for these advancements is the improvement in research tools--sophisticated imaging devices, for example, like PET scans and MRI, that penetrate the complicated architecture of the brain. And laboratory techniques, like one that can remove living brain tissue from rats and keep it alive in a petri dish for hours, allowing researchers to manipulate and probe live brain cells. The goal is to understand the biology of memory in the same thorough way that bodily functions like digestion or blood circulation are understood. They're not there yet. But they're getting closer.

In his untidy office in one typical cognitive lab on the campus of the University of California, Irvine, about sixty miles south of Los Angeles, Richard Granger, computer scientist, psychologist, and professor of neurobiology, emphasizes how key memory is for humans to function.

"A lot of people think of memory solely in terms of recalling past events, like your childhood," says Granger. "But memory is so much more than that. If you lose your memory, the whole fabric of your individuality is eroded, your whole perspective on the world is lost.

"For example, how do you know how to walk or drive a car? Those are motor skills your body memorizes but we never consciously think about. How do you know how to get home, how do you remember the name of your wife, or the guy you work with who's down the hall? And from what mental hat do you pull-- instantly--the language you need to spontaneously communicate with someone?"

The list of examples that highlight the complexity and peculiarity of memory is endless. You can vividly recall from years past that first kiss from a high school sweetheart, but can't find where you left your car keys the night before. You bump into someone you haven't seen in ten years and instantly remember his name, but when you look up a phone number in the directory, you forget it before you can pick up the phone and dial.

Besides factual recall, memory is the tool that organizes the world for you, putting what you experience on a daily basis into a context that can be understood. You spy a three-foot-high, furry, four-legged animal with a tail and know it's a canine. It's not the foot-high, four-legged furry animal with a tail we call a cat, or, for that matter, the slightly larger version with similar characteristics we know as a sheep. Further, we know that this particular canine is a domesticated dog, not a similar looking wolf or coyote. Finally, you recognize its sable fur, white throat, and remarkable resemblance to Lassie, and categorize this animal as a collie, and not a basset hound or German shepherd.

Neurobiologists like Granger tend to describe the brain as a computer, a vast network of tens of billions of neurons--nerve cells--that interact. "Except it's not an accurate comparison," he says. "You take the most powerful supercomputer known, but you have to remember it was built by the human brain; it's the brain that is the most complex thing in the universe." One square millimeter of the cortex, the brain's crinkly surfaced dome, contains some eighty thousand nerve cells. This almost unimaginable number of neurons raises the stereotypical situation of having more of something than we can possibly use. "The truth is," says Granger, "we could live a hundred lifetimes and never fully use our brain."

"That's probably how that old canard got started about how we only use ten percent of our brain's capacity," he continues. "That's not true. All the parts of our brain are working all the time. Memories are stored all over the place; the hippocampus, for example, is where the first inputs from the outside world are registered, and where short-term memories reside. Later, more long-term memories are moved into the cerebral cortex; emotions are contained in still another spot, the amygdala--love, fear, stuff like that."

The neurobiology lab at Irvine is just one of dozens around the country that are trying to dissect the various aspects

of memory. As they burrow deeper into the brain, disagreements have risen over the nuances of how memories form. One thing all agree on, though, is that it all begins in the cell.

Granger characterizes the process that leads to memory formation as a "cascade of events," each leading rhythmically to the next. Neurons are the basic units of the nervous system. The cascade begins when sensory neurons throughout the body respond to a stimulus from the environment--an odor picked up by the nose, a pressure upon the skin, light striking the retina of the eye--and send the stimulus on to the hippocampus, a pair of wishbone-shaped structures that lie roughly between the ears. The neuron translates the stimulus into an electrochemical pulse, a kind of code comprised of electrical impulses (in science-speak, this pulse is known as a cell's "action potential"). The cells obtain their electrical voltages from ions--charged particles that are common in most body fluids. The neuron receives the pulse through its dendrites, webs of fibers, thousands strong, that resemble the branches of a tree. The dendrites funnel the signal on to the body of the cell. If the signal is strong, or "robust," enough, the pulse shoots down the cell's output system, or axon.

Each of the axon branches terminate close to another neuron's dendrites, forming an infinitesimally small gap between the two. This gap is the synapse, and, when the pulse reaches the end, or terminal, of the axon, it becomes the pulse's job to leap that tiny gap (less than a micron across) and get to the dendrites of the neuron next door.

Here's where chemistry kicks in. In simplified form, when the pulse hits the terminal, it breaks open small containers called vesicles that release neurotransmitters, messenger molecules that ferry the ions across the synaptic gap. The main neurotransmitter involved in memory formation is glutamate (although dozens of other neurotransmitters exist). The glutamate causes the membrane of the receiving neuron to welcome the transported ions with open arms.

Once embraced, various reactions take place, not all of which are fully understood. There is much cross-talk, for example, in the form of chemical signal-swapping, that takes place between the passing and receiving neuron. Special "gates" then open that allow the electrical charges to pass into the receiving cell and build in strength. If the charge is strong enough, this neuron also fires--the cascade of events starts all over again. A single neuron, in fact, can receive multiple signals from thousands of other neurons; in turn, its axon can branch repeatedly, transmitting the pulse to thousands of fellow neurons. And all of this activity takes place in no more than a few thousandths of a second.

But where does an actual memory form? Initially, in the hippocampus. If an outside stimulus is robust enough, whole groups of neighboring brain cells inside the hippocampus eventually align together to form a unique structure. That structure will then respond as a single entity when the same stimulus comes again. Neurobiologists call this phenomenon "long- term potentiation," or LTP, and it's what makes memory possible. In other words, says Granger, a physical change rapidly takes place in the brain. "Someone introduces himself to you by name, and in a second or less that name's been encoded into a string of altered electrochemical connections among whole arrays of neurons. And conceivably, the change could last as long as you live." Every experience makes a change. If the outside sensory signal is weak (a phone number from information), the memory will last a short time; if the outside signal is strong (your child's first steps), the memory may last forever.

Over time, though, even neurons involved in LTP can be weakened or rewritten as new memories, similar to the old, "overwrite" upon existing neuronal structures. Neuronal structures all interconnect as well; that's why memories can be confusing or wrong--they have combined with other memories. A stimulus from the environment also can invoke an existing memory. Smell is a big culprit of this, and is probably the oldest of the senses, most likely appearing some 3.5 billion years ago. All of us have experienced the power of odors to evoke a memory.

No one, though, has actually seen a memory form. But through inference and circumstantial evidence, theories abound. And, as always in basic research, disagreement exists between scientists over which theory is right or wrong. While there is widespread agreement as to how it is transmitted from neuron to neuron, it is still anybody's guess as to how memory is created in the first place.

Currently, the strongest explanation for how memory forms was first developed in 1984 by Granger's colleague, Gary Lynch, another Irvine-based neuroscientist. Scientists know that calcium is part of the fluid that bathes the neurons. Lynch argues that when a receiving cell opens its receptors to allow in the flood of electrical charges, calcium pours in, too. Somehow, the calcium triggers an enzyme called calpain inside the cell that, until now, has been inactive. Enzymes are chemicals in the body that serve as catalysts, causing chemical reactions in organisms. But calpain is not your ordinary enzyme, but one of a class called "proteases" that specifically chop up proteins.

Lynch believes that's what calpain does for memory: it instantaneously tears down a cell's protein framework, or cytoskeleton, thereby altering the existing glutamate receptors, thus altering the existing brain circuitry as well. This begins the process of memory. "This kind of permanent change is really counterintuitive in biology," Granger points out, "because the body likes to keep things in balance. Your temperature rises, you sweat to cool off. You cut your finger, the immune system kicks in to fix it. Cells die, and are replaced. Yet here's the brain, building new structures, instantaneously, that are often permanent."

But change alone is not all that's involved in memory. There's also storage. Like the dog example, the brain shuffles memories into various categories. We group tall, boxy shapes with doors and glass windows that we see into the category "buildings." Other categories place them into skyscrapers, storage sheds, or homes.

And some researchers now believe that for a period of weeks, memories that eventually become long-term remain stored in the hippocampus before being shipped out to the cortex, the surface of the brain. The cortex, in turn, distributes the various "pieces" of a memory throughout the brain--sound goes to its auditory section, sight to the visual section, and so on. It also maintains long synaptic connections to other regions of the brain, like the amygdala. The emotional effects of memory are stored here; whenever you recall something, your cortex checks with the amygdala, setting off the appropriate emotion for that memory. Further, at the front of the cortex is an area involved in coordinating physical movement, from judging a fly ball to sprinting down a track. Still another connection reaches a region known as the striatum, where movement is organized, allowing us to duck from a flying object without having to make the conscious decision to do so.

All of these sections are wired together by synapses, connections that allow these various areas to talk to one another and form associations. It's the reason why you can close your eyes and mentally "walk" down the hall of your house, out the front door, and down your street, all the while accurately recalling what is located where, colors, and how things smelled and what sounds you heard the last time you physically walked there.

What, indeed, would life be like without memory? It would be much like Amy's life. At the age of eighteen, Amy (a pseudonym) was stricken by an unknown disease that left her with global amnesia. The only memories she retains today are those she accumulated up to the age of eleven. Like H.M., she can no longer learn facts. Still, she speaks all three languages she spoke before contracting her disease, and she can read and write.

For eight years, UC-Irvine neurologist Arnold Starr and his wife, Bonnie Olson, a psychologist, worked with Amy, developing a "step-by-step" program to try and give her at least some small degree of independence. With it, Amy must write down, then follow, every single step she needs to take to achieve even the simplest task. Starr believes that endless repetition of these steps has finally tapped into Amy's procedural, or implicit, memory. Remarkably, Amy can now cook, wash, and even do word processing on a computer. She has written about her current state, and the pride she takes in maintaining some degree of independence:

* I can cook myself.

All my recipies [sic] are all written in the same way. The quantity, the material that I need and the recipie step by step.

* I can go to do my shopping all alone.

I have in all my cupboards sheets of paper telling me what are the things I use with a square where I have to write a cross when I need something.

* I can go everywhere.

I can with a plan or with an address go everywhere with a public bus or by walk. I have a plan with me which tells me where I have to go and at which time.

With their biological inquiries, scientists like Granger, Lynch, Starr, and others worldwide are slowly gaining insights into how the brain works. A few months ago, Lynch and his colleagues at Irvine even announced the development of a drug that enhances memory in rats. Clinical trials are expected to begin before the end of the year. For people stricken with diseases like Alzheimer's--diseases that kill billions of synapse --the drug may eventually help by boosting the response of those synapses that remain. Still, there's a long, long way to go.

"There'll come a day when we'll know, without quarrel, everything there is to know about the biological aspects of memory," says Richard Granger. "But even when we do, we still won't really know memory. There are just too many things that happen as we walk around that aren't involved or explained at the level of the neuron. Really, we've only just begun."

Mark Wheeler is a freelance science writer based in Los Angeles.

Wheeler, Mark. "Snapshots from the Brain: How Memories Are Made." *Destination Discovery*. Oct. 1994: 14-19. *SIRS Researcher.* Web. 30 Sep 2010.